INFECTIVE ENDOCARDITIS 2006: INDICATIONS FOR SURGERY

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ABSTRACT

Infective endocarditis has challenged clinicians for centuries. Despite recent advances in diagnosis and therapy, the risks of major complications and death in many clinical situations remain unacceptably high, related in part to patient demographics and the changing microbiology of the disease. Surgery in the acute phase is indicated chiefly for the treatment of heart failure, the eradication of intra-cardiac abscess or the management of antibiotic-resistant infection. Surgery for the prevention of systemic embolization in patients with large vegetations is an evolving area of clinical practice that will merit continued scrutiny as surgical repair techniques, anesthetic management and perioperative patient outcomes steadily improve in high volume centers. The strength of treatment recommendations is limited by the absence of prospective, randomized controlled trial data, a limitation that applies broadly to the field of valvular heart disease. Ongoing multi-center registry efforts will help fill several important knowledge gaps.

Introduction

The term, infective endocarditis (IE), refers to an active intra-cardiac infection that resides on one or more heart valve surfaces. Other cardiac structures can be primarily or secondarily involved, including chordae tendineae, mural endocardium, myocardium and pericardium. Endovascular infection can also occur at more remote sites in the circulation, in association with aortic coarctation, patent ductus arteriosus or surgically constructed vascular shunts. Despite several recent advances in diagnosis and treatment, IE still poses a serious risk for major morbidity and death. Successful management will require combined medical/surgical treatment in as many as 25% of patients in the acute phase of the illness. Recognition of the evolving indications for surgery is a critical component of clinical decision-making in the modern era. Patient education and the selective use of antibiotic prophylaxis are the mainstays of prevention.

Epidemiology and Prognosis

The incidence of IE has increased over the past several decades, particularly among patients 65 years of age or older (1). Depending on

the demographics of the population studied, incidence rates range from 2 to 10 cases per 100,000 person-years (2–5). In 2006, the American Heart Association reported 29,000 hospital discharges and 2370 deaths with IE as a primary or secondary diagnosis (6). Factors contributing to this upward trend include the aging of the population, an increase in the prevalence of degenerative valvular heart disease and the more widespread use of implanted heart valve substitutes and intra-cardiac devices. There are increasing numbers of patients with chronic, predisposing medical conditions, such as diabetes, HIV infection and end-stage renal disease (7). Nosocomial infection, most commonly due to central venous line-related bacteremia, has become increasingly problematic. *S. aureus* is now the most common cause of both community- and hospital-acquired IE world-wide (8). Antibiotic resistance poses additional challenges.

Patients with IE are an extremely heterogeneous group with varying co-morbidities, causative organisms and complications. Accurate prognostic classification may help inform individual treatment decisions. Chu and colleagues analyzed 267 consecutive cases of definite IE with an overall mortality of approximately 20% and found the following factors to be independently predictive of death: diabetes mellitus, *S. aureus* as a causative organism, an embolic event and an increased APACHE II score (9). Data obtained from the International Collaboration on Endocarditis (ICE) have corroborated the finding that diabetes mellitus is independently associated with higher mortality in IE (10). Hasbun and colleagues derived and externally validated a prognostic classification system for adults presenting with complicated left-sided native valve IE (11). In both a derivation and validation cohort, the 6-month mortality rate was approximately 25%. Five baseline clinical features were significantly associated with 6-month mortality: increased Charlson co-morbidity score, abnormal mental status, moderate to severe heart failure, causative organism other than *S. viridans* and medical therapy without valve surgery. Using these prognostic features, the authors derived a weighted scoring system that classified patients into four groups with progressively increasing 6-month mortality risk, ranging from 5 to 70% (Figure 1). In a separate analysis, Fowler and colleagues analyzed 300 cases of definite *S. aureus* IE unrelated to injection drug use who were enrolled in the International Collaboration on Endocarditis—Prospective Cohort Study and found the following factors to be independently associated with in-hospital death: advanced age, stroke and persistent bacteremia (8). Another study of *S. aureus* native valve endocarditis (NVE) from the ICE-merged database found advanced age, heart failure, perian-

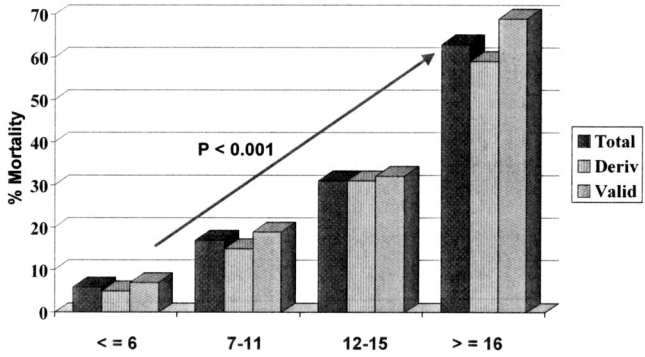

FIG. 1. Relationship between 6-month mortality and prognostic classification system (point score) of adults with complicated left-sided native valve endocarditis. Five baseline clinical features independently associated with 6 month mortality were used to construct the scoring system: patient co-morbidity, abnormal mental status, moderate to severe heart failure, bacterial etiology other than viridans streptococci, and medical therapy without valve surgery. Integer scores were modified by linear transformation of the parameter coefficient taken from logistic regression and then rounded to the nearest integer. Adapted with permission (11).

nular abscess formation and absence of surgical therapy to be associated with higher mortality (12). Thuny and colleagues performed TEE in 384 consecutive patients with IE (13). In addition to age, female gender, serum creatinine $>$ 2.0 mg/dl, moderate or severe heart failure and infection with *S. aureus*, vegetation length $>$ 1.5 cm was an independent predictor of 1 year mortality (Figure 2). Total mortality at 1 year was 20.6% in this study. Although the decision to undertake early surgery for the treatment of IE must be made on an individual

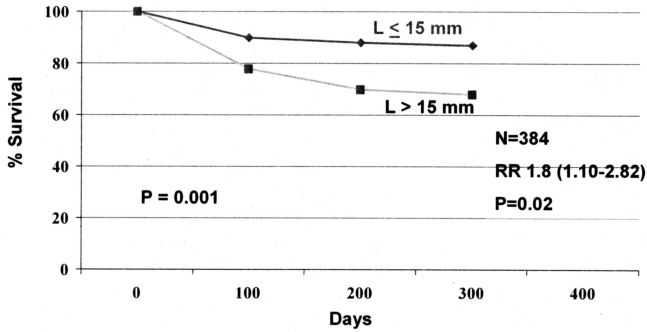

FIG. 2. One-year survival among 384 consecutive patients with infective endocarditis according to vegetation length (L) as measured by TEE. Reproduced with permission (13).

basis, these data provide a useful means to target aggressive medical and surgical interventions to high-risk patient groups.

Indications for Surgery

The current indications for surgery during the acute phase of IE have evolved empirically (Tables 1 and 2) (14). There are no prospective, randomized controlled trial data on which to rely, and recommendations have been derived primarily from expert consensus. For patients with NVE, the primary indication for surgery in the acute phase is the development of heart failure from either valve regurgitation or stenosis. Evidence of elevated LV end-diastolic or left atrial pressures by either invasive (catheter) or noninvasive (echo/Doppler) assessment

TABLE 1
Indications for Surgery for Native Valve Endocarditis

Class I

1. Surgery of the native valve is indicated in patients with acute infective endocarditis who present with valve stenosis or regurgitation resulting in heart failure. *(Level of Evidence: B)*
2. Surgery of the native valve is indicated in patients with acute infective endocarditis who present with AR or MR with hemodynamic evidence of elevated LV end-diastolic or left atrial pressures (e.g., premature closure of MV with AR, rapid decelerating MR signal by continuous-wave Doppler (ν-wave cutoff sign), or moderate to severe pulmonary hypertension). *(Level of Evidence: B)*
3. Surgery of the native valve is indicated in patients with infective endocarditis caused by fungal or other highly resistant organisms. *(Level of Evidence: B)*
4. Surgery of the native valve is indicated in patients with infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (*e.g.,* sinus of Valsalva to right atrium, right ventricle, or left atrium fistula; mitral leaflet perforation with aortic valve endocarditis; or infection in annulus fibrosa). *(Level of Evidence: B)*

Class IIa

Surgery of the native valve is reasonable in patients with infective endocarditis who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy. *(Level of Evidence: C)*

Class IIb

Surgery of the native valve may be considered in patients with infective endocarditis who present with mobile vegetations in excess of 10 mm with or without emboli. *(Level of Evidence: C)*

Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Valvular Heart Disease). American College of Cardiology Website. Available at: http://www.acc.org/clinical/guidelines/valvular/index.pdf

TABLE 2
Indications for Surgery for Prosthetic Valve Endocarditis

Class I

1. Consultation with a cardiac surgeon is indicated for patients with infective endocarditis of a prosthetic valve. *(Level of Evidence: C)*
2. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with heart failure. *(Level of Evidence: B)*
3. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with dehiscence evidence by cine fluoroscopy or echocardiography. *(Level of Evidence: B)*
4. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with evidence of increasing obstruction or worsening regurgitation. *(Level of Evidence: C)*
5. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with complications, for example, abscess formation. *(Level of Evidence: C)*

Class IIa

1. Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with evidence of persistent bacteremia or recurrent emboli despite appropriate antibiotic treatment. *(Level of Evidence: C)*
2. Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with relapsing infection. *(Level of Evidence: C)*

Class III

Routine surgery is not indicated for patients with uncomplicated infective endocarditis of a prosthetic valve caused by first infection with a sensitive organism. *(Level of Evidence: C)*

Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Valvular Heart Disease). American College of Cardiology Website. Available at: http://www.acc.org/clinical/guidelines/valvular/index.pdf

may also prompt surgery. Valve surgery is indicated for treatment of fungal or other highly resistant organisms, and for treatment of intracardiac abscess, perforation, fistulous tracts and false aneurysms. Surgery is reasonable for patients with recurrent emboli and persistent vegetations and for patients with persistent bacteremia despite several days (5–7) of appropriate antibiotic therapy in the absence of a metastatic focus of infection. Surgery to prevent embolization can be considered for treatment of large (> 1.0 cm), mobile vegetations, particularly in large volume surgical centers with expertise in primary valve repair. This latter issue remains controversial, though improvements in repair techniques and surgical outcomes have warranted re-evaluation. Most echocardiographic studies have shown a relationship between vegetation size and the risk of embolization, particularly for

lesions affecting the anterior mitral valve leaflet (15,16). Embolization risk increases significantly with vegetation size greater than 1.0 cm and may also vary as a function of organism- and patient-specific attributes (16,17). Because this risk appears to decrease precipitously following institution of appropriate antibiotic therapy, prophylactic surgery to prevent embolization should be performed early in the course of the infection. As implied by the TEE study of Thuny et al, very large vegetations ($>$ 1.5 cm) may also be a reason to consider surgery independent of the severity of the valve dysfunction, the presence or absence of heart failure or the imputed risk of embolization (13) (Figure 2). Prior to undertaking operation, the members of an experienced surgical team should concur that the likelihood of successful repair is high. In many instances, repair constitutes vegetectomy, debridement, eradication of abscess cavities and pericardial patch repair of the underlying defect. Leaflet resection, placement of an annular ring or both might be required, as dictated by the intraoperative findings. Valve replacement is necessary when there has been extensive destruction of intra-cardiac structures. The increased peri-operative and long-term risks associated with valve replacement, compared with valve repair, mandate a higher threshold for its performance, especially when surgery is being considered for prevention of embolization rather than for treatment of heart failure or intra-cardiac abscess. Advances in surgical techniques for management of endocarditis, such as homograft root replacement for complicated aortic valve endocarditis, are beyond the scope of this brief review.

In an attempt to clarify the benefit of surgery, Vikram and colleagues retrospectively analyzed 513 cases of complicated left-sided NVE from seven Connecticut hospitals (18). Complicated IE was defined by the presence of one of the following features for which valve surgery might be considered in current clinical practice: heart failure, new valvular regurgitation, refractory infection, systemic embolization to vital organs or presence of a vegetation on echocardiography. In this non-randomized study, 45% of patients underwent valve surgery and 55% received medical therapy alone. In the unadjusted analysis, valve surgery was associated with a significant reduction in six-month mortality (16% vs. 33%, $p < 0.001$). In their propensity analysis, performed to account for confounding due to selection bias, surgical therapy remained significantly associated with a lower six-month mortality (hazard ratio 0.40; 95% CI, 0.18–0.91; $P = 0.03$). The association between valve surgery and reduced mortality was apparent *only* for those patients with moderate or severe heart failure (Figure 3). Pa-

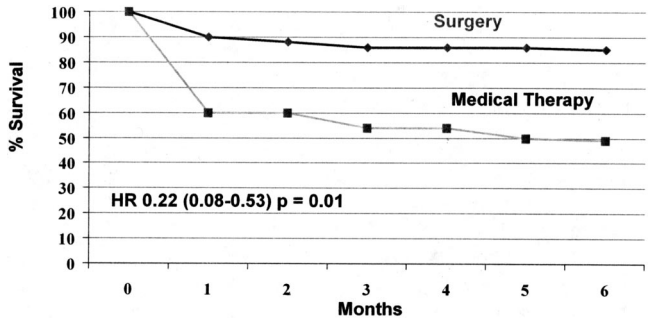

FIG. 3. Six-month survival among patients with complicated left-sided native valve endocarditis and moderate to severe heart failure receiving medical or surgical therapy. Among propensity matched patients with moderate to severe heart failure, valve surgery was associated with a significant reduction in mortality compared with medical therapy (HR 0.22, 95% CI 0.08–0.53, p = 0.01). Reproduced with permission (18).

tients meeting other criteria for the definition of complicated left-sided NVE did not appear to gain a survival benefit from surgery.

The indications for surgery in patients with prosthetic valve endocarditis (PVE) are similar. Surgery is recommended for patients with heart failure, a poorly responsive microorganism, peri-valvular extension or an unstable prosthesis. Prosthetic valve dehiscence is defined as a rocking motion of the valve with excursion of 15 degrees or more in at least one plane. Peri-valvular abscess formation is more common with PVE than with NVE, because the infection typically involves the interface between the sewing ring and surrounding tissue. Early surgery may be considered for selected patients with PVE without peri-valvular extension or heart failure. For example, *S. aureus* PVE is rarely eradicated with antibiotics alone, and retrospective analyses suggest that combined medical and surgical therapy is more effective than medical therapy alone (19). PVE that relapses after appropriate antibiotic therapy should lead to a careful search for peri-valvular extension and metastatic foci of infection. Some patients with relapsed PVE may respond to a second course of antimicrobial therapy, but the majority will require surgery for cure. Despite the frequent need for surgery, medical cure with antibiotic therapy should be attempted initially for uncomplicated PVE caused by first infection with a sensitive organism (e.g., bioprosthetic PVE with enterococci or streptococci).

The timing of surgery following CNS embolization in patients with either native or prosthetic valve endocarditis is problematic, due to the risk of hemorrhagic transformation. It is generally advisable to wait up to 5–7 days after bland CNS infarction and as long as 4 weeks after primary CNS hemorrhage (e.g., from a ruptured mycotic aneurysm)

before undertaking cardiac surgery (20). Mycotic aneurysms require primary attention and exclusion with either percutaneous or neurosurgical techniques.

Peri-operative mortality risk varies with age, pre-operative LV dysfunction, prosthetic vs. native valve involvement, type and complexity of surgery (repair vs. replacement), the extent of intra-cardiac infection, embolic complications, infecting organism (particularly *S. aureus*) and patient co-morbidities. Older surgical series have reported mortality rates of 5–25% for patients with IE treated surgically (21–25). More recent series in selected patients, however, provide a more optimistic outlook. Zegdi et al reported a peri-operative mortality rate of 3% among 37 consecutive patients who underwent mitral valve repair with the Carpentier technique for active endocarditis between 1989 and 1994 (26). Ten-year survival in this series was 80% and freedom form mitral re-operation 91%. Yankah and colleagues reported peri-operative mortality rates of 9.3% and 14.3%, respectively, among 161 patients requiring elective/urgent and emergency aortic root homograft reconstruction for complex endocarditis (27). Early and late residual/recurrent infection occurred in 4.3% of patients. Seventeen-year survival was 70.4 +/− 3.6%.

Approach to the Patient

Once suspected on clinical grounds, the diagnosis of IE must be pursued vigorously with appropriate blood cultures and echocardiography. Trans-thoracic echocardiography (TTE) is routine. Trans-esophageal echocardiography (TEE) is recommended for patients with high-risk clinical features at presentation (e.g., suspected *S. aureus* infection of the native aortic valve/root), known congenital heart disease, suspected PVE or suboptimal/non-diagnostic TTE images (15). Some analyses have suggested that in patients with an intermediate pre-test likelihood of IE, an initial TEE is a cost-effective means of diagnosis and may obviate the need for routine TTE. Intra-operative TEE is indicated for patients undergoing cardiac surgery. Early surgical consultation is warranted, with a collaborative assessment of the indications for surgery in the acute phase, based largely on the clinical, echocardiographic and hemodynamic data reviewed above. The urgency of surgery is predicated on the patient's hemodynamic status. Acute severe aortic regurgitation is poorly tolerated and usually mandates surgery within 24 hours. Patients with acute severe mitral regurgitation can often be stabilized with intensive medical therapy with deferral of surgery for up to several days. Once heart failure

intervenes, however, surgery should not be inordinately delayed to provide time for pre-operative antibiotic therapy.

Outcome is most intimately related to pre-operative left ventricular function and the severity of heart failure. The type of surgery is dictated by the intra-operative findings and the skill of the surgeon. Patients must complete 4–6 weeks of postoperative antibiotic therapy and receive careful instructions regarding the need for life-long prophylaxis.

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DISCUSSION

DuPont, Houston: Does the size of any one vegetation vary according to the offending organism? I think in group B streptococcal infections, for example, the vegetations are larger than one would expect.

O'Gara, Boston: Some are well known for their propensity to form large vegetations; for example, *H. influenzae*, *H. parainfluenzae*, fungi, and others. Size probably relates to the organism and to the host response.

Dismukes, Birmingham: I would like to congratulate you on a very balanced and thoughtful presentation, even though you are a cardiologist and there are many of us here who are infectious diseases specialists. You've taken a very nice approach to a very difficult problem. Control studies, as you've emphasized, are very difficult to perform and we have to use the total approach that you have outlined. Certain centers have been very aggressive. I have been at one through the years that has taken an aggressive approach to this disease, both for native valve endocarditis and prosthetic valve endocarditis, and I think the trend, over the last decade and a half or so, has been to operate earlier and more often. We do need better data. The studies are coming forth, as you have mentioned, and I think we need to keep an open mind about this and particularly to use valve repair techniques or other approaches that don't involve total valve replacement. So, we need more data, but your comments are appreciated.

O'Gara: Thank you.

Southwick, Gainesville: No, exactly right, and I would echo what Bill Dismukes said. Your aggressive approach I completely concur with, and we actually consult cardiology and cardiac surgery day one on every single patient because of these concerns. The major problem I have is to convince the surgeons that there is a very low risk of recurrent infection in the newly implanted valve. What is the reference for the 2% incidence you quote? Most people say there are no data, and they will not operate for six to seven days, and often the patient detriorates with worsening heart failure to the extent that surgery becomes a less viable option.

O'Gara: I think the take home message is that the risk is small and that the risk of death in the setting of heart failure is high and depending upon the experience of the surgeon and the surgical team, it's time to move ahead. Valve repair techniques have evolved to the extent that we should be able to assuage our surgeons that the risk of infection is even lower than that small number.

Southwick: Yes, I would point out that what they are doing is they are debriding and removing bacteria that should hasten the cure of the infection.

O'Gara: It's a cancer operation.

Karchmer, Boston: Pat, that was a lovely talk, and thank you very much. The 2% figure comes from a review, as you know, of cases going to surgery with positive blood cultures within 48 hours of surgery or positive valve cultures and then having a very low incidence of recurrent disease (Olaison L, Pettersson G. Cardiol Clin 21:235, 2003). The point I wanted to make was the propensity analysis (Vikram 2003), and that may have slipped by a lot of people, but that's an analysis where you select patients and you match them for the indication of needing surgery, and then you do a multivariate analysis in these matched pairs to look at the impact of the variable. There is now another study, which is in press, which has not isolated heart failure per se, but many of the other surgical indications that you've called to the floor, that has shown that surgical intervention in a propensity analysis matched-pair situation, indeed, benefits outcome. So, we are getting there. It's very slow and there are now multi-center registries trying to address this. So I think the data are on the way. Very nicely done.

O'Gara: Thank you.

Friesinger, Nashville: Pat, thank you. Masterful presentation. A clinical question-What's the experience with metastatic infectious lesions in the current era of treatment of endocarditis?

O'Gara: So is your question what is the incidence of embolization in the . . .

Friesinger: In other words, we treat the valve surgically very frequently now. All of us have had the experience of having a metastatic lesion appear in the brain or kidney. So, how frequent is that?

O'Gara: It's very frequent, but I think it depends on how carefully you look for evidence of embolization. Studies that have relied on clinical symptoms or signs of embolization report rates of 40%; studies that use CT imaging of brain, spleen, mesentery, spine, et cetera report higher rates, closer to 50 to 60%. So embolization is a very common accompaniment of endocarditis, particularly in its early phase. Thank you very much.